Neurovascular Coupling

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August 26, 2014

Neuron Network Model

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August 27, 2014

Background

1. Why are we studying the neuron network model?
2. What did we study for the neuron network model?

Model Description

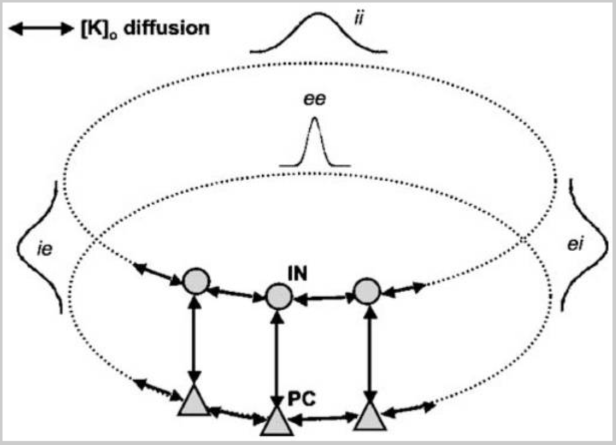
1. Single Neuron Dynamics
2. Neuron Network Dynamics

Model Description

Physical Parameters Of The Neurons Considered

1. Voltage, Sodium, Potassium, Chlorine, Calcium,
2. Gating Variables n and h.

Network Schismatic



Model Description

Difference between single and network neuron model

1. Leak Current
2. Synaptic Current
3. Potassium

Single Neuron

- Current Equations:

$$I_{Na} = -g_{Na}[m_\infty(V)]^3 h(V - V_{Na}) - g_{NaL}(V - V_{Na}).$$

$$I_K = -(g_K n^4 + \frac{g_{AHP}[Ca]_i}{1 + [Ca]_i})(V - V_K) - g_{KL}(V - V_K).$$

$$I_{Cl} = -g_{ClL}(V - V_{Cl}).$$

$$I_{pump} = (\frac{\rho}{1 + exp((25.0 - [Na]_i)/3.0)})(\frac{1.0}{1.0 + exp(5.5 - [K]_o)}).$$

$$I_{glia} = \frac{G_{glia}}{1.0 + exp((18 - [K]_o)/2.5)}.$$

$$I_{diff} = \epsilon([K]_o - k_{0,\infty}).$$

Single Neuron

- Differential Equations:

$$C\frac{dV}{dt} = I_{Na} + I_K + I_{Cl}\,.$$

$$\frac{dq}{dt} = \phi[\alpha_q(V)(1-q) - \beta_q(V)q], q = n, h\,.$$

$$\frac{d[Ca]_i}{dt} = \frac{-0.002g_{Ca}(V - V_{Ca})}{1 + exp(-(V + 25)/2.5)} - [Ca]_i/80\,.$$

$$\frac{d[K]_o}{dt} = -0.33I_K - 2\beta I_{pump} - I_{glia} - I_{diff}\,.$$

$$\frac{d[Na]_i}{dt} = 0.33\frac{I_{Na}}{\beta} - 3I_{pump}\,.$$

Single Neuron

- Supporting Equations:

$$m_\infty(V) = \alpha_m(V)/(\alpha_m(V) + \beta_m(V)) .$$

$$\alpha_m(V) = 0.1(V + 30)/(1 - exp(-0.1(V + 30))) .$$

$$\beta_m(V) = 4exp(-(V + 55)/18)) .$$

$$\alpha_n(V) = 0.01(V + 34)/(1 - exp(-0.1(V + 34))) .$$

$$\beta_m(V) = 0.125exp(-(V + 44)/80)) .$$

$$\alpha_h(V) = 0.07(-(V + 44)/20) .$$

$$\beta_h(V) = 1/[1 + exp(-0.1(V + 4))] .$$

Neuron Network

- Current Equations:

$$I_{Na}^{e/i} = -g_{Na}[m_{\infty}^{e/i}(V^{e/i})]^3 h^{e/i}(V^{e/i} - V_{Na}^{e/i}) .$$

$$I_K^{e/i} = -(g_K[n^{e/i}]^4 + \frac{g_{AHP}[Ca]_i^{e/i}}{1 + [Ca]_i^{e/i}})(V^{e/i} - V_K^{e/i}) .$$

$$I_L^{e/i} = -g_L(V^{e/i} - V_L^{e/i}) .$$

$$I_{syn}^e = -\frac{(V_j^e - V_{ee})}{N} \sum_{k=1}^{N} g_{jk}^{ee} s_k^e \chi_{jk}^e - \frac{(V_j^e - V_{ie})}{N} \sum_{k=1}^{N} g_{jk}^{ie} s_k^i \chi_{jk}^i .$$

$$I_{syn}^i = -\frac{(V_j^i - V_{ei})}{N} \sum_{k=1}^{N} g_{jk}^{ei} s_k^e \chi_{jk}^e - \frac{(V_j^i - V_{ii})}{N} \sum_{k=1}^{N} g_{jk}^{ii} s_k^i \chi_{jk}^i .$$

Neuron Network

- Current Equations Cont'd:

$$I_{pump}^{e/i} = \left(\frac{1.25}{1 + exp((25.0 - [Na]_i^{e/i})/3.0)}\right)\left(\frac{1.0}{1.0 + exp(8.0 - [K]_o^{e/i})}\right).$$

$$I_{glia}^{e/i} = \frac{G_{glia}}{1.0 + exp((18 - [K]_o^{e/i})/2.5)}.$$

$$I_{diff}^{e/i} = \epsilon([K]_o^{e/i} - k_{0,\infty}).$$

- Differential Equations:

$$C\frac{dV^{e/i}}{dt} = I_{Na}^{e/i} + I_{K}^{e/i} + I_{L}^{e/i} + I_{syn}^{e/i} + I_{ext}^{e/i} + I_{rand}^{e/i}\,.$$

$$\tau^{e/i}\frac{ds^{e/i}}{dt} = \phi\sigma(V^{e/i})(1 - s^{e/i}) - s^{e/i}\,.$$

$$\frac{d\eta^{e/i}}{dt} = \gamma^{e/i}(V^{e/i} - V_b) - \tilde{\gamma}\eta^{e/i}\,.$$

$$\frac{d[K]_o^{e/i}}{dt} = 0.33 I_K^{e/i} - 2\beta I_{pump}^{e/i} - I_{diff}^{e/i} - I_{glia}^{e/i} + \frac{D}{\Delta x^2}$$
$$([K]_{o(+)}^{e/i} + [K]_{o(-)}^{e/i} + [K]_o^{i/e} - 3[K]_o^{e/i})\,.$$

$$\frac{d[Na]_i^{e/i}}{dt} = 0.33\frac{I_{Na}^{e/i}}{\beta} - 3 I_{pump}^{e/i}\,.$$

Neuron Network

- Supporting Equations:

$$\sigma(V^{e/i}) = 1/[1 + exp(-(V^{e/i} + 20)/4)] .$$

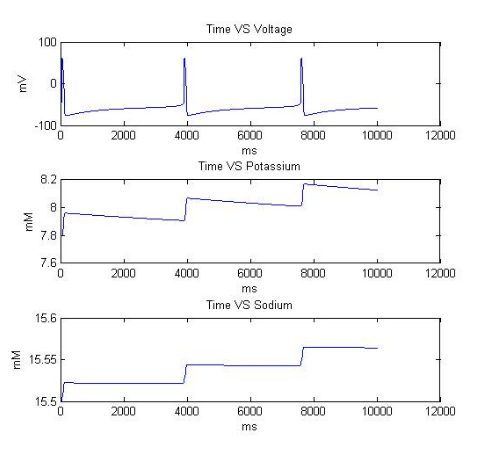
$$\chi_{jk}^{e/i} = \begin{cases} exp(-\eta^{e/i}/v) & \eta^{e/i} > 5.0 \\ 1 & otherwise \end{cases}$$

$$\gamma^{e/i} = \begin{cases} 0.4 & -30 < V^{e/i} < -10 \\ 0 & otherwise \end{cases}$$

$$V_L^{e/i} = 26.64 ln(\frac{[K]_o^{e/i} + 0.065[Na]_o^{e/i} + 0.6[Cl]_i^{e/i}}{[K]_i^{e/i} + 0.065[Na]_i^{e/i} + 0.6[Cl]_o^{e/i}}) .$$

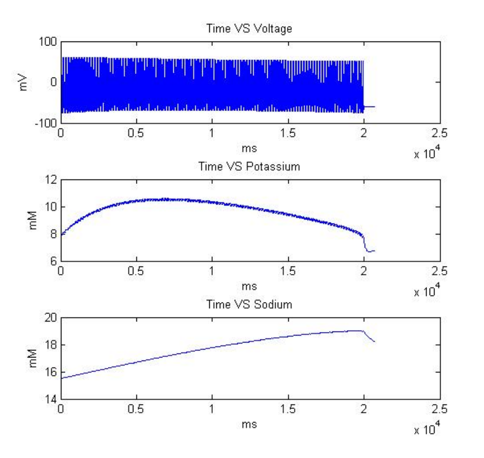
Single Neuron Simulation Results

The dynamics of membrane voltage, sodium, potassium at 100 ms.



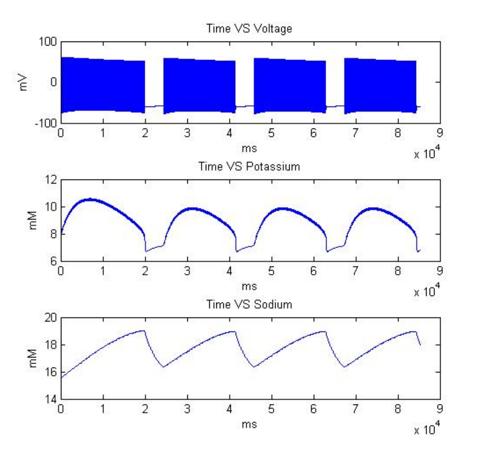
Single Neuron Simulation Results

The dynamics of membrane voltage, sodium, potassium at 10000 ms.



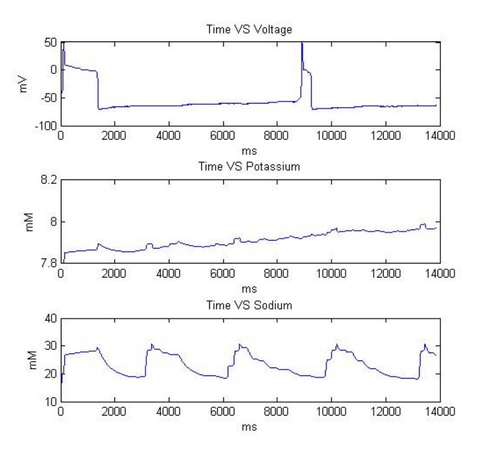
Single Neuron Simulation Results

The dynamics of membrane voltage, sodium, potassium at 100000 ms.



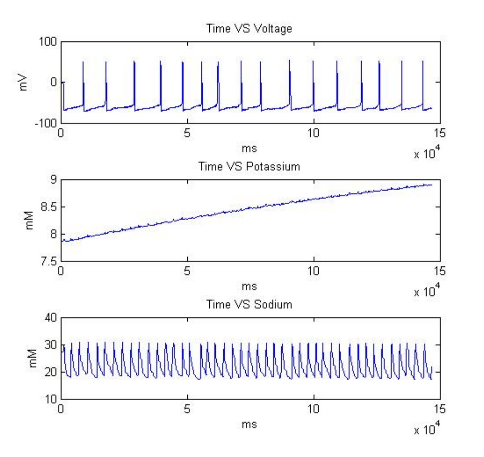
Neuron Network Simulation Results With 5 Neurons

The dynamics of first neuron's membrane voltage, sodium, potassium at 100 ms.



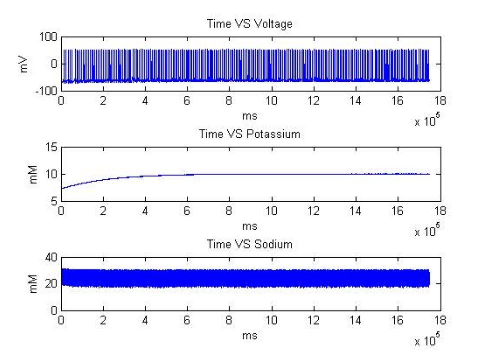
Neuron Network Simulation Results With 5 Neurons

The dynamics of first neuron's membrane voltage, sodium, potassium at 1000 ms.



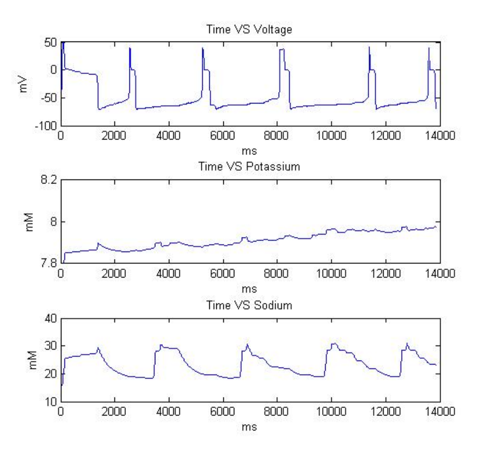
Neuron Network Simulation Results With 5 Neurons

The dynamics of first neuron's membrane voltage, sodium, potassium at 10000 ms.



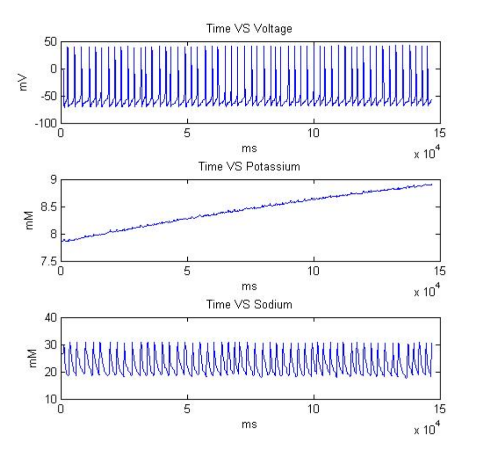
Neuron Network Simulation Results With 5 Neurons

The dynamics of third neuron's membrane voltage, sodium, potassium at 100 ms.



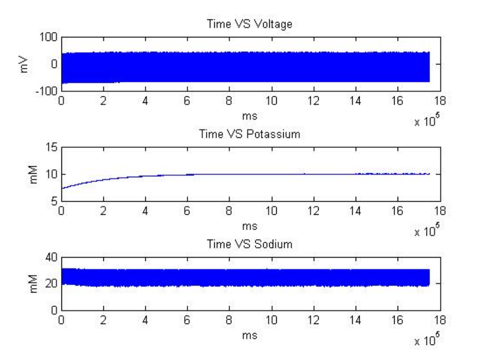
Neuron Network Simulation Results With 5 Neurons

The dynamics of third neuron's membrane voltage, sodium, potassium at 1000 ms.



Neuron Network Simulation Results With 5 Neurons

The dynamics of third neuron's membrane voltage, sodium, potassium at 10000 ms.



Circulation Model

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August 26, 2014

FETAL HYPOXIA: WHAT IS IT?

- Episodes of low oxygenation in the fetus
- Often caused by occlusion of the umbilical cord, especially during labour
- Triggers deceleration of the fetal heart

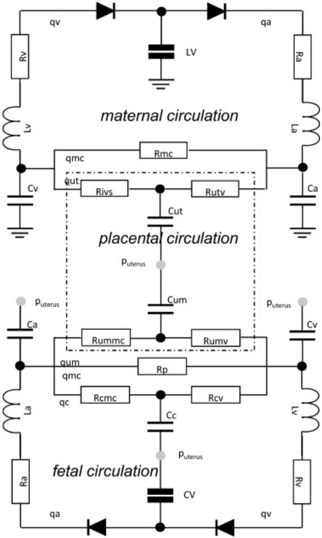
FETAL HYPOXIA: WHY STUDY IT?

- Tissues need steady supply of oxygen to stay alive
- Oxygen deprivation lowers blood pH and can lead to brain damage, but can also be asymptomatic
- Currently diagnosed based on fetal heart rate, but this is not a reliable predictor of whether the hypoxia is damaging
- Modelling fetal circulation could lead to better understanding, diagnostic methods

THE BEATRIJS MODEL

- Combines previously published models of various components of the maternal and fetal cardiovascular system:
  - Sarcomere movement in the maternal and fetal hearts [Bovendeered, et al (2006)]
  - Oxygen diffusion and partial pressure in the fetus [Sa Couto, et al (2002)]
  - Uterine contractions during labour [Rodbard, et al (1963), Fung, et al (1997)]
  - Blood flow through the maternal and fetal circulatory systems
  - Regulatory changes to the fetal heart rate in response to low [Metcalfe, et al (1967)] oxygen concentration

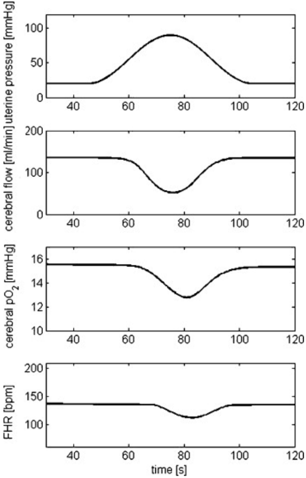
THE BEATRIJS MODEL



TESTING BEATRIJS: OVINE EXPERIMENTS

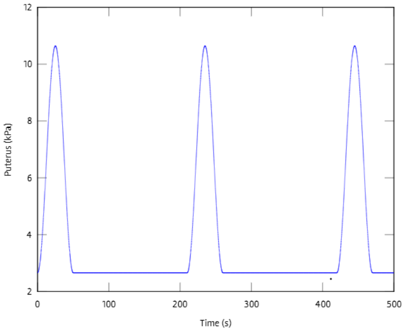
- Sheep umbilical cords fitted with devices designed to cause occlusions
- Occlusions of increasingly large magnitude induced in late- term sheep fetuses periodically, interspersed with rest periods
- Fetal biological parameters measured and compared with output of Beatrijs model
- Majority of graphs output from Beatrijs model deemed realistic by panel of gynaecologists

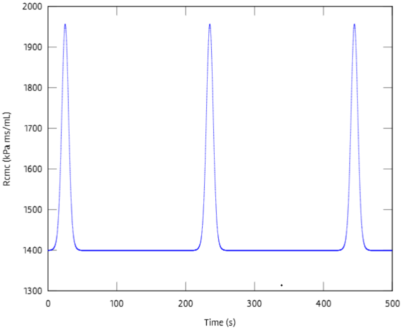
TESTING BEATRIJS: OVINE EXPERIMENTS



TESTING BEATRIJS: REPRODUCING THE MODEL

- Uterine contractions successfully reproduced





TESTING BEATRIJS: REPRODUCING THE MODEL

- Difficulty reproducing the rest of the models results:
    - Initial conditions used by Beatrijs not stated in paper
    - Circuit diagram describing arrangement, properties of model components inaccurate
    - Erroneously printed equations
    - Discrepancies, implicit contradictions between published volume parameters
    - Paper unclear on models treatment of retrograde blood flow during expansion phase of each heartbeat
    - Authors known to have used Euler Method to numerically solve system; unclear whether they discretized the system in the process

Citations

- Beatrijs van der Hout-van der Jagt, et al *A mathematical model for simulation of early decelerations the cardiotocogram during labor*
- Beatrijs van der Hout-van der Jagt, et al *Insight into variabel fetal heart rate declarations from a mathematical model*
- Bovendeered PHM, et al *Dependence of intramyocardial pressure and coronary flow on ventricular loading and contractility: a model study*
- Sa Couta, et al *Mathematical model for educational simulation of the oxygen delivery to the fetus.*
- Rodbard S, et al *Transmural pressure and vascular resistance in soft-walled vessels.*
- Fung, et al *Biomechanics: circulation*
- Metcalfe J, et al *Gas exchange in the pregnant uterus*

Data Analysis Part

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August 26, 2014

Background and Motivation

Fetus is connected with mother body by umbilical cord. Mother brings oxygen and other nutrients to fetus via umbilical cord. However, umbilical cord might be blocked in the process of labor. In case of blocking, fetus doesn't have adequate oxygen or other necessary elements. Therefore, it might damage fetal bodily functions especially brain functions.

Background and Motivation

Outputs from mathematical model

- Heart Rate (HR)
- Blood Pressure (BP)
- Pressure of Oxygen (PO)
- Pressure of CO_2 (PCO_2)
- EEG and ECoG

Question : How those biomarkers affect each other ?

Statistical Method

Generalized Additive Model

$$HR = f_1(BP)+f_2(PO)+f_3(PCO_2)+f_4(BP*PO)+f_5(BP*PCO_2)+f_6(PCO_2*PC$$

Local Polynomial Regression Model

$$HR = h_1(EEG) + h_2(ECoG) + h_3(EEG * ECoG)$$

each f and h are smoothing function need to be approximated. Multiplication terms stand for interactive effect between those two bio-marker.

Statistical Method

- Each f and h can be approximated by smoothing method (smoothing spline)
- Each functional effect also can be tested whether they are statistically significant or not

Model1: Qiming's simulation data

For Qiming Wang's model, it is modeling HR, BP, PO and PCO_2. However, there might be something missing is the model. But, we don't know what they are. The missing part might significantly affect outputs. Therefore, we manually delayed some parts in the model. Let's denote the reduced model as WD and denote the original model as WOD. We want to compare the differences between outputs of those two models.

Results

For WOD, all six functional effect is statistically significant (all p-value ¡ 0.001). It means BP, PCO_2 and PO did affect HR. Moreover, we can't separately consider BP, PCO_2 or PO themselves because there were three interaction terms. Among BP PCO_2 and PO, the effect of each of them on HR always depends on the other two. For WD, if we just con- sidered three main effect BP, PCO_2 and PO, BP was not statistically significant (p-value $=$ 0.09). However, if we included three interaction terms, all six functional effects were significant.

Questions?